REMARKS

Upon entry of the foregoing amendment, claims 1-11, 13-20, and 22-25 are currently pending, with claim 12 canceled without prejudice to, or disclaimer of, the material contained within, and claims 21 and 26-50 withdrawn by the Examiner under 35 U.S.C. § 121 as allegedly being drawn to distinct inventions. Of the originally filed claims, claims 1-2, 4-20, and 22-25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification, and claims 1-20 and 22-25 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claims 1-20 and 22-25 also stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 4,997,834 to Muro et al., in view of the Merck Manual of Diagnosis and Therapy. Also, claims 1-20 and 22-25 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over an article by Yoshii et al., American J. Respiratory Cell and Molecular Biology, 20:1190-1200, 1999, in view of EP 0956865 to Uehata, further in view of Merck.

The amendment to claim 1 incorporates the description of formula I or a functional derivative thereof from claim 3. The amendment to claim 3, adds the description that the Rho activity inhibited to increase intracavernosal blood pressure relative to mean arterial pressure is in an organ subject to sexual stimulation. This amendment is supported by the experiments described in Example 2, pages 25-26 of the specification showing an increase in intracavernosal blood pressure in the rat penis. Additional amendments to the claims change the dependency of the claims as required by the amendment of claim 1 or involve minor changes in syntax. Also, claim 25 is amended to remove the phrases "certain" and "such as those" as suggested by the Examiner. Accordingly, no new matter is added by the amendment of the claims.

The Rejection of Claims Under 35 U.S.C. § 112, First Paragraph, Is Traversed Or Rendered Moot

The Examiner rejected claims 1-2, 4-20, and 22-25 as allegedly not enabled under 35 U.S.C. § 112, first paragraph. Thus, the Examiner stated that:

> Claims 1-2, 4-20, and 22-25 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular compound such as Y-27632 disclosed in the specification (see Figure 2 for example) in co-administering the particular compounds such as sodium nitroprusside or NOR-1 employed in methods for particular treatments herein, does not reasonably provide enablement for the administration of any compounds represented by "a compound which attenuates RhoA and/or RhoB kinase activity to sexual stimulation" alone or in combination with any compounds represented by "a compound that inhibits binding of GTP to RhoA enzyme" or "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", or "a second compound which potentiates the effects of nitric oxide", for the claimed methods of treating male or female sexual dysfunction.
>
> These recitations, "a compound which attenuates RhoA and/or RhoB kinase activity to sexual stimulation", "a compound that inhibits binding of GTP to RhoA enzyme", "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", and "a second compound which potentiates the effects of nitric oxide" in these claims, are seen to be merely functional language.

Office Action at page 3. The Examiner went on to review the claimed invention in light of the eight factors cited by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). Without in anyway acquiescing to the Examiner's arguments, Applicants have amended independent claim 1 to incorporate the description of a compound of formula I or a functional derivative thereof. Thus, the claim describes a specific compound or a functional derivative thereof that can attenuate RhoA and/or Rho-kinase activity in an organ, such as the penis, that is subject to sexual stimulation. Also, Applicants have canceled claim 12 without prejudice to, or disclaimer of, the subject matter contained within.

With respect to claims 7-9 describing the use of compounds that reduce the amount of active Rho-kinase activity, Applicants have described in the specification that guanine nucleoside dissociation inhibitors, such as known guanine nucleoside dissociation inhibitors RhoGDI-I, II, or III, bind cytosolic RhoA to inhibit the release of GDP from RhoA thus promoting the active state of RhoA. See the specification at page 15, lines 15-24. Also, with respect to claim 10, Applicants describe that it is known in the art that compounds such as sodium nitroprusside may be used to inhibit translocation

of Rho A to the membrane. See the specification at page 30, lines 10-16. Also, cAMP-dependent protein kinase has been implicated in inhibiting RhoA translocation.

Also, with respect to claim 11, Applicants describe working examples of using compounds known to potentiate the effects of NO, such as NOR-1 and sodium nitroprusside, to add to the effects of Y-27632. See e.g., Example 5, pp. 30-31, describing the experiments shown in Figures 6 and 7.

Applicants therefore respectfully assert that no more than routine (i.e., not undue) experimentation would be required to practice the methods of amended claims 1-11, 13-20, and 22-25. Thus, it is respectfully asserted that the rejection of claims 1-20 and 22-25 as not enabled under 35 U.S.C. § 112, first paragraph is rendered moot and thus, should be withdrawn.

The Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph, Is Traversed Or Rendered Moot

The Examiner rejected claims 1-20, and 22-25 as allegedly not enabled under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse the rejection for the reasons stated below.

The Examiner stated that the recitations "an organ subject to" and "an individual" as used in claim 1 are indefinite. Applicants used these terms in the context of their ordinary dictionary meanings, and respectfully assert that it is unclear as to why further definition is required. For example, as defined in the Oxford Dictionary and Thesaurus (American Edition, Oxford University Press, 1996) "an individual" is "a single human being" or "a person". Also, the phrase "an organ subject to sexual stimulation" is meant to describe an organ, commonly defined as "a self-contained part of an organism having a special vital function" (see e.g., Oxford Dictionary and Thesaurus, American Edition, Oxford University Press, 1996) that physiologically responds to a sexual stimulus. An example of how an organ subject to sexual stimulation responds to a sexual stimulus is provided at page 1 of Applicants' specification, describing that one common aspect of the sexual response in males and females is the vasoactive response, which results in engorgement of the sexual tissues of the genitalia with blood as a result of vascular

smooth muscle relaxation in response to sexual stimulation. See the specification at page 1, lines 20-29.

The Examiner further stated that the recitation "a functional derivative" is not clearly defined in the specification and thus, is indefinite. Applicants have used the word "functional" in the context of its ordinary dictionary meaning defined as "of or serving a function" (see e.g., Oxford Dictionary and Thesaurus, American Edition, Oxford University Press, 1996). Applicants have also used the word derivative in light of its common meaning used in the chemical arts as "a chemical compound that is derived from another" (see e.g., Oxford Dictionary and Thesaurus, American Edition, Oxford University Press, 1996). Thus, Applicants respectfully assert that a functional derivative is a compound derived from formula I that has the same biological function as the compounds of formula I. Common functional derivatives are the various salts and hydrates of formula I. Also included are compounds having modified functional groups where the modification does not reduce the functional activity. For example, derivatives of the compounds of formula I are described in U.S. Patent No. 4,997,834 to Muro (compounds A, B, and C, described in cols. 8-9). Such derivatives would comprise functional derivatives for Applicants' invention if shown to be effective in attenuating RhoA or Rho-kinase activity in an organ subject to sexual dysfunction. Further, Applicants specifically describe that a functional derivative comprises a compound which can inhibit the activity of Rho-kinase mediated phosphorylation and thereby increase intracavernosal blood pressure (ICP) relative to mean arterial pressure (MAP). See e.g., Applicants specification at page 8, lines 7-10. Thus, Applicants respectfully assert that the meaning of a "functional derivative" as used in the specification and claims is not indefinite under 35 U.S.C. § 112, second paragraph.

The Examiner further stated that the recitation "others" in claim 12 and "certain drugs" in claim 25 renders the claims indefinite. Applicants have canceled claim 12, without prejudice to, or disclaimer of, the matter contained therein. Also, Applicants' have amended claim 25 to remove the phrase "certain drugs".

The Examiner further stated that the term "potentiates" in claim 11 renders the claim indefinite. Applicants respectfully assert that the term "potentiates" is also used in the context of its ordinary dictionary meaning defined as "to make more powerful, to

increase the effectiveness of" (see e.g., Oxford Dictionary and Thesaurus, American Edition, Oxford University Press, 1996). As described in Applicants' specification at page 2, it is known that certain compounds act to increase the erectile response by enhancing (or potentiating) the effect of local NO release in the penis. For example, the compound sildenafil (Viagra) is a type 5 phosphodiesterase inhibitor that potentiates the effects of local release of NO, thereby resulting in vascular smooth muscle relaxation (see Applicants' specification at page 2, lines 23-25). Another example of biochemical "potentiation" is provided in Example 3, page 17 of Applicants' specification, where Applicants show administration of Y-27632 into the cavernous sinuses "potentiates" the CCP/MAP response to ganglionic stimulation at each voltage (FIG. 3B, open bars) and Example 5, describing figure 6, where Applicants show that inhibition of Rho-kinase with Y-27632 potentiates the erectile response resulting from the NO donor drug NOR-1.

The Examiner further asserted that use of a broad range or limitation together with a narrow range or limitation that falls within the broad range renders claims 12 and 25 indefinite. Applicants respectfully note that claim 12 has been canceled, and that claim 25 is amended to delete the phrase "such as" in an attempt to make the claim more clear.

For the reasons stated above, it is respectfully asserted that claims 1-20 and 22-25 are not indefinite under 35 U.S.C. § 112, second paragraph, and that the rejection be withdrawn.

The Rejection of Claims Under 35 U.S.C. § 103(a) Is Traversed Or Rendered Moot

The Examiner rejected claims 1-20, and 22-25 under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 4,997,834 to Muro et al. (hereinafter "US '834 to Muro") in view of the Merck Manual of Diagnosis and Therapy (hereinafter "Merck"). Thus, the Examiner stated that

> Muro et al. discloses that the compounds of formula (I) which has covered and encompassed the elected specie, Y-27632 (also known as (+)-(R)-trans-4-(1-aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride monohydrate, see abstract, col.2, col.8 lines 1-17 and 41-49) are useful in methods of treating hypertension and abnormal of smooth muscles (see col.1 lines 17-24) since these active compound possess coronary and cerebral blood flow-increasing activities (see col.8 lines 19-

> 27). Muro et al. discloses the effective dose of the compound with a pharmaceutically acceptable carrier to be administered to a hypertensive male (see col.8 lines 53 to col. 10 line 25).
>
> Muro et al. does not expressly disclose the employment of the particular Y-27632, in methods of treating male or female sexual dysfunction. Muro et al. does not expressly disclose the method further comprising the active agent herein.
>
> The Merck Manual of Diagnosis and Therapy (17th ED) teaches that vascular disorders such as hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can result in erectile dysfunction (a known sexual dysfunction) (see page 1836 the right column). The Merck Manual of Diagnosis and Therapy (17th ED) also teaches that a nitric oxide is useful in treating erectile dysfunction or sexual dysfunction caused by vascular disorders.
>
> . . .
>
> One having ordinary skill in the art at the time the invention was made would have been motivated to employ to employ the particular compound of Muro et al. in methods of treating male or female sexual dysfunction, because the particular compound of Muro et al is known to be useful in methods of treating hypertension and abnormal of smooth muscles (see col.1 lines 17-24) since these active compound possess coronary and cerebral blood flow-increasing activities according to Muro et al.
>
> . . .
>
> Therefore, one of ordinary skill in the art would have reasonably expected that the particular compound of Muro et al., would have beneficial therapeutic effects and usefulness in methods of treating male or female sexual dysfunction, by increasing coronary and cerebral blood flow- activities and smooth muscle relaxation, and also treating hypertension, and diabetes mellitus, atherosclerosis in patients suffering therefrom.

Office Action at pp. 11-13 (emphasis in original).

Applicants respectfully assert that the Examiner has not made out a *prima facie* case of obviousness. As noted by the Examiner, Muro et al. describes that compounds of formula I and derivatives thereof (see e.g., test compounds A, B, and C in U.S. 834 to Muro, cols. 8-9) may increase coronary and cerebral blood flow. Nowhere in Muro et al., however, is there an indication that compounds of formula I may be used to inhibit the activity of Rho-kinase. Applicants' specification teaches that compounds of formula I have a specific, targeted action – that of inhibiting Rho kinase in the penis or other sexual

organs to increase local (e.g., intracavernosal) blood pressure relative to mean arterial pressure (MAP). It is the ability of these compounds to specifically increase blood flow in the sexual organ of interest while *not* substantially increasing systemic blood flow that provides the ability for these agents to specifically ameliorate sexual dysfunction. In contrast, Muro et al. and Merck suggest that compounds of formula I would be expected to have wide-ranging effects on systemic blood flow such as reducing hypertension and/or increasing coronary blood flow. It is not clear that it would be beneficial to increase coronary and cerebral blood flow while attempting to treat sexual dysfunction. Applicants' invention teaches that it is possible to increase blood flow in an organ subject to sexual stimulation while leaving mean arterial pressure (i.e., coronary and cerebral blood flow) within baseline ranges.

Applicants respectfully assert that the cited references actually teach away from Applicants' invention. Reading US '834 to Muro in view of Merck, one would be discouraged from using compounds of formula I and functional derivatives thereof to treat sexual dysfunction. First, the references provide no evidence that compounds of formula I are effective in treating sexual dysfunction. In contrast, Merck teaches away from using compounds of formula I to treat sexual dysfunction. Thus, Merck suggests that nitric oxide, shown in Applicants' specification to work independently of Rho kinase inhibitors, may be effective for treating erectile dysfunction. In addition, there is no evidence provided in the cited references that compounds of Formula I interact with an enzyme (i.e., Rho kinase) in sexual organs to provide a specific effect. Thus, prior to the immunostaining results described in Applicants specification showing Rho kinase enzyme in the penis, it was unknown that compounds of formula I would have a site of action in the penis (or other sexual organs). Also, based on the broad activity profile of compounds of formula I as described in Muro, it would not be expected that compounds of formula I would have the ability to specifically increase intracavernosal blood pressure in an organ subject to sexual stimulation while leaving mean arterial pressure (i.e., coronary and cerebral blood flow) within baseline ranges.

The Examiner further stated that claims 1-20 and 22-25 are unpatentable under 35 U.S.C. § 103(a) over Yoshii et al., *American J. Respiratory Cell and Molecular Biology*,

20:1190-1200, 1999 (hereinafter "Yoshii") in view of EP 0956865 to Uehata (hereinafter "Uehata"), further in view of Merck.

Thus, the Examiner stated that:

> Yoshii et al. discloses that the instant elected specie, Y-27632 (also known as (+)-(R)-trans-4-(1-aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride monohydrate, see abstract) is the particular compound that attenuates RhoA kinase activity which can increase smooth muscle relaxation (see abstract). Yoshii et al. discloses that GTP is useful in combination with Y-27632 (see the abstract).
>
> Yoshii et al. does not expressly disclose the employment of the particular Y-27632, in methods of treating male or female sexual dysfunction. Yoshii et al. does not expressly disclose the method further comprising the active agent herein.
>
> Uehata (EP 0 956 865) discloses that the compounds of formula (III) which are structurally similar to Y-27632, as being RhoA kinase inhibitors, are useful in treating hypertension, vascular contraction, asthma in which smooth muscle contraction is involved and also treating fertilization and nidation of fertilized egg (see page 3 lines 13-20 and 30-34, page 8 lines 14-39).
>
> The Merck Manual of Diagnosis and Therapy (17th ED) teaches that vascular disorders such as hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can result in erectile dysfunction (a known sexual dysfunction) (see page 1836 the right column). The Merck Manual of Diagnosis and Therapy (17th ED) also teaches that a nitric oxide is useful in treating erectile dysfunction or sexual dysfunction caused by vascular disorders.

Office Action at pp. 13-14. The Examiner concludes that:

> [O]ne of ordinary skill in the art would have reasonably expected that the particular compound Y-27632 would have beneficial therapeutic effects and usefulness in methods of treating male or female sexual dysfunction, by increasing coronary and cerebral blood flow- activities and smooth muscle relaxation, and also treating hypertension, and diabetes mellitus, atherosclerosis in patients suffering therefrom.

Office Action at 15 (emphasis in original).

Applicants respectfully assert that although Yoshii describes that Y-27632 has the ability to inhibit Rho kinase, these results are described for rabbit tracheal and human

bronchial smooth muscle treated in vitro. There is no description in Yoshii of Rho kinase activity in organs subject to sexual stimulation, such as the penis. Also, Yoshii teaches that the mechanism for relaxation of smooth muscle contraction is complicated and that studies from one organ (or enzyme system) cannot be extrapolated to studies in other systems (see e.g., Yoshii at page 1191, col. 1, describing that the mechanism of action of different agonists varies in canine tracheal as well as rabbit vascular and ileum smooth muscle). Thus, reading Yoshii, even in light of Applicants' findings described in the specification that Rho kinase is found in cavernosal tissue (see Applicants' specification, Example 1, pp. 24-25), it is not clear that Y-27632 could be used to specifically increase blood flow in a sexual organ.

Applicants also respectfully assert that Uehata does not remedy the deficiencies of Yoshii. As noted by the Examiner, Uehata describes that compounds similar in structure to compounds of formula I inhibit Rho kinase and are useful in treating hypertension, vascular contraction, and asthma. Thus, Uehata merely describes that in some cases, compounds having a structure similar to formula I may also be used to inhibit Rho kinase. Nothing in Uehata, in combination with Yoshii teaches or suggests using Y-27632, or functional derivatives thereof, to specifically inhibit Rho-kinase in organs subject to sexual stimulation. Finally as described above, Merck teaches away from use of compounds of formula I to treat sexual dysfunction. Thus, Merck suggests the use of nitric oxide, shown in Applicants' specification to work independently of Rho kinase inhibitors, to treat erectile dysfunction.

Applicants note that the discovery the compounds of formula I may be used to treat sexual dysfunction was considered to be a significant and nonobvious finding in the scientific community as evidenced by the award to one of the inventors (K. Chitaley) of the Jean-Paul Geniste Award for Best Basic Science Paper, 9th World Congress, International Society for Sexual and Impotence Research, Perth, Australia, October 17-21, 2000, based on these findings. In addition, several of the inventors have be invited to be guest speakers at national and international meetings regarding their discovery (e.g., Invited speaker, R. Clinton Webb, "What makes vascular smooth muscle contract and relax? Three guesses," Molecular Mechanisms of Erectile Function; International Society for Sexual and Impotence Research, Rome, Italy, September 29, 2001; Invited

speaker, Thomas Mills, "Inhibition of tonic contraction, a new way to treat erectile dysfunction?" Symposium on Molecular Basis of Endocrine Physiology, American Society of Andrology, Annual Meeting, 2002; Invited speaker, R. Clinton Webb, "Ying yang of corporal smooth muscle control," 11th World Congress, International Society for Sexual and Impotence Research, Buenos Aires, Argentina, October 17-21, 2004; Invited speaker: Christopher J. Wingard, Rho-kinase sensitization in cavernosal smooth muscle, Experimental Biology, 04, Washington, D.C.).

Thus, Applicants respectfully assert that Muro in view of Merck, and/or Yoshii in view of EP 0956865 and further in view of Merck, does not suggest nor enable Applicants' invention, as is required for a determination of obviousness under 35 USC 103(a). *See e.g., Motorola, Inc. v. Interdigital Technology Corp.*, 43 U.S.P.Q. 2d 1481, 1489 (Fed. Cir. 1997) (quoting *Beckman Instruments, Inc. v. LKB Produkter AB*, 13 U.S.P.Q. 2d 1301, 1304 (Fed. Cir. 1989) (holding that in order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method). There is no absolutely no suggestion, teaching or description in any of these references of the use of Rho kinase inhibitors to increase local blood flow in an organ subject to sexual stimulation in such a manner as to locally increase blood flow with minimal systemic effects.

Further, the Federal Circuit has held that the totality of a reference's teachings must be considered in finding whether the reference in fact suggests the invention in question, or teaches away from the invention in question. *W.L. Gore & Assocs. V Garlock, Inc.*, 220 USPQ 303, 311 (Fed. Cir. 1983). As described above, reading both US '834 to Muro and Merck, one would be discouraged from trying to use compounds of formula I to treat erectile dysfunction.

To establish a prima facie case of obviousness three criteria must be met: (i) a suggestion or motivation to modify or combine references; (ii) a reasonable expectation of success; and (iii) all the limitations in the claim(s) must be taught or suggested by the reference, or combination of references. MPEP 706.02(j). Applicants respectfully assert that none of the references cited by the Examiner alone, or in combination, teach all of the limitations of Applicants' claimed invention. Nor is there any suggestion, upon reading these two references, to combine the references in a way that teaches Applicants'

invention. Also, because US '834 to Muro and Merck teach away from using compounds of formula I to treat erectile dysfunction, even if there were some motivation to modify or combine the references, there would not be a reasonable expectation of success. Thus, Applicants respectfully assert that these the cited references do not render Applicants' claimed invention unpatentable under 35 U.S.C. §103(a).

For at least the above reasons, Applicants respectfully assert that the Examiner has not made a prima facie case of obviousness and that as amended, the claims are patentable over the cited references. Thus, it is respectfully requested that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone the undersigned at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

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